PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	**Sinan Tas**
Application No.:	**10/682584**
Filed:	**October 9, 2003**
For:	**USE OF CYCLOPAMINE IN THE TREATMENT OF BASAL CELL CARCINOMA AND OTHER TUMORS**
Examiner:	**James D. Anderson**
Group Art Unit:	**1614**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Docket No.: T80.2H-11341-US01

Correction Letter

The patent applicant has discovered omissions in two sentences found on pages 17 and 19 of the Reply to the outstanding rejection filed 21 January 2001. The corrections are not believed to be substantive, but their correction is believed to clarify the involved sentences involved s in response to the Office Action dated December 10, 2009.

Replacement pages 17 and 19 are enclosed with the additions shown in double underlining (*i.e.* not for intended emphasis).

Please enter and consider the enclosed replacement pages when considering the reply.

Respectfully submitted,
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Date: February 10, 2010

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medicament claims are not functionally related to the claimed product, claims 58-59 and 64-67 are anticipated by Dudek et al'516. The rejections are traversed. Dudek et al'516 does not anticipate any of said claims and does not anticipate for multiple reasons.

(*i*) In the *Gulack* case, the Court decided allowance of a product claim where a new and unobvious functional relationship was found between the printed matter and substrate of it. In the *Ngai* case, *Ngai* had described a new method of amplifying and normalizing RNA and claimed a kit for normalizing and amplifying an RNA population, comprising previously known compounds and instructions describing *Ngai*'s method. The Court, like the *Gulack* Court, looked to see whether there exists any new and unobvious functional relationship between the printed matter and the substrate. Finding none, the Court affirmed rejection of *Ngai*'s claim to the kit.

Both cases that have been referred by the Examiner support patentability of present claims 58-59, 64-67. As noted in item I.2 above, instructions are implicit or inherent for prescription drugs and are legally mandated in the U.S.A. and most other states throughout world. Notice that in case of *Ngai*, amplified-normalized RNA populations were prepared in prior art by methods other than *Ngai*'s new method. *Ngai* developed a new method to obtain amplified-normalized RNA; the end result (amplified-normalized RNA) is the same as in prior art. In the present situation, however, content of instructions is functionally related to the product and it is also clear that previously unknown and unobvious technical effects and therapeutic results are obtained by following the instructions. Without the instructions of present medicament claims, a skilled person does not obtain described apoptosis of the tumor cells and does not obtain the therapeutic results that follow and that are recited in the claims. In prior art, a skilled person using a medicament described by Dudek et al'516 would obtain an inhibition of Hedgehog signaling in tumor cells and would obtain an inhibition of tumor growth through inhibition of tumor cell proliferation (see the 03.18.2009 amendment for analysis of Dudek et al'516 as a whole; see said and previous amendments also for analysis of the rest of prior art). However, the facts on record show that causation of an inhibition of proliferation effect on tumor cells by use of a selective inhibitor of Hh/Smo signaling does not make differentiation or apoptotic elimination of the same cells anticipated or obvious (see e.g. the 03.18.2009 amendment). It is further clear that the therapeutic results recited in claims 58-59 and 64-67 cannot be achieved by causation of an several different mitogenic signals were found to act on GSK3β to downregulate it and to relieve the GSK3β substrate proteins from GSK3β mediated phosphorylation and proteolysis (see e.g. Diehl AJ et al, *Genes & Development* 1998;12:3499-3511). Since the substrates of GSK3β included cyclin D1 and β-catenin (which is required for Wnt/β-catenin signaling), it was clear that this kinase could regulate responses to multiple signals promoting cellular proliferation (Diehl et al, *ibid*). Similarly, it was well recognized that whereas phosphorylation of Ci/Gli proteins by PKA promotes their proteolytic processing to inhibit transcription of Hh target genes, upregulated PKA phosphorylates many other proteins as well and PKA certainly lacks a selective action on Hh/Smo signaling (see e.g. Wang et al, *ibid*). For decades, it was common knowledge in prior art that binding of cyclic AMP (cAMP) to PKA activates its kinase (phosphorylating) activity. Further, many hormones were known to affect cellular cAMP content and changes in cellular cAMP content were known to affect numerous cellular functions. Thus, it was clear in prior art that a single obligatory transducer (Smo) and a single end point (Ci/Gli) make Hh/Smo signaling ideally suited to selective inhibition but cAMP or analogs or "agonists" thereof or PKA or GSK3β are unsuitable. Dudek et al'516 does not describe use of a selective inhibitor of Hh/Smo signaling to obtain a presently described and claimed technical effect or therapeutic result and its claims are directed to uses of a "cAMP agonist".

(***iv***) Presently claimed invention is not inherently present in prior art. Inhibition of proliferation of various cell types, including tumor cells, by treatment with a selective inhibitor of Hh/Smo signaling was known in prior art. See e.g. Fujita E et al, *Biochemical and Biophysical Research Communications* 1997;238:658-664 referred to in Dudek et al'516 (col. 44, line 64 to col. 45, line 11) describing a dose-dependent inhibition of proliferation of human lung cancer cells by treatment with a selective inhibitor of Hh/Smo signaling. No induction of differentiation or apoptosis of said tumor cells is described even though the proliferation-inhibited tumor cells were examined by microscopy which ordinarily allows detection of said effects when caused. See the 03.18.2009, 02.20.2008, 06.11.2007 and 01.10.2007 dated amendments and the Declaration attached to the latter showing that use of a selective inhibitor of Hh/Smo signaling to achieve inhibition of proliferation of tumor cells does not provide differentiation and/or apoptosis of the tumor cells and that a treatment schedule and dose far beyond that produces inhibition of proliferation of tumor